REMARKS

Claims 1-3, 7-8 and 11-107 are pending in this application. Claims 11-49, 52-59, 62, 64-70, 73, 76-82, 85 and 87-89 have been withdrawn from consideration deemed non-elected subject matter. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 78, 83-84, 86 and 90-107 were variously rejected under 35 U.S.C. § 112, first paragraph. Claims 1, 7, 50-51, 60-61, 71-72, 83-84 and 90-93 were variously rejected under 35 U.S.C. § 112, second paragraph. Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 75, 83-84, 86 and 90-107 were rejected under 35 U.S.C. § 102(b). Claims 50, 60, 71, 72 and 83 have been variously objected to.

By this amendment, claims 1-3, 7-8, 43-62, 87, 90-93 and 102-105 have been canceled, claims 63, 71, 72, 75, 83 and 84 have been amended and new claim 108 has been added without prejudice or disclaimer of any previously claimed subject matter. Support for the amendments can be found, *inter alia*, throughout the specification. Support for the amendments to claims is found, *inter alia*, at page 36, line 22. Support for new claim 108 is found, *inter alia*, at page 72, line 31, to page 73, line 2.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Drawings

The drawings filed with the application have not been approved. Enclosed herewith is a submission of formal drawings.

Claim Objections

Claims 50, 60, 71, 72 and 83 have been variously objected to. The objections have been herein addressed in the amendments. Applicants respectfully request withdrawal of the claim objections.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86 and 90-107 were variously rejected under 35 U.S.C. §112, first paragraph. Applicants respectfully traverse these grounds for rejection.

On September 30, 2002, Applicants elected "Amb a1" as the specific antigen and "AACGTTCG" as the specific ISS at the Examiner's request. In the rejections of the current Office Action, the Examiner goes well beyond this specific antigen and this specific sequence in describing the subject matter allegedly not enabled and allegedly not supported by written description. From this, it appears that the specific antigen and sequence have, in some cases, been deemed enabled and/or adequately described and the Examiner has moved on to examine the generic claims. Accordingly, Applicants have herein addressed these wider rejections both in the amendments and in the remarks.

Enablement

Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86 and 90-107 were rejected for allegedly not enabling any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims. Applicants respectfully traverse this rejection.

The amended claims are directed to populations of conjugate molecules which are defined by both structural and functional characteristics. The populations of conjugate molecules comprise antigens and polynucleotides. Antigens are well known in the art and extensively described in the specification. The claimed polynucleotide is greater than 6 and less than about 200 nucleotides in length and comprises an immunostimulatory sequence (ISS) comprising the sequence 5'-C, G-3'. Applicants respectfully submit that the specification enables the skilled artisan to make and/or use the claimed conjugate populations.

The Examiner states that "it would require undue experimentation even for one skilled in the art to practice the claimed invention." Office Action, page 10. Applicants respectfully disagree with this conclusion.

The claimed conjugate populations are described throughout the specification. The working examples in the specification (pages 71-86) exemplify populations of the conjugate molecules as claimed. In addition, examples of ISS-containing polynucleotides and methods for their synthesis are provided, for example, on pages 36-43. Examples of antigens of use in the claimed compositions are provided, for example, on pages 43-50. Examples of ways to couple the ISS-containing polynucleotide and antigen to generate the claimed conjugate populations are provided, for example, on page 30-32 and 50-53. Means of assessing the structural and functional characteristics of a population of conjugate molecules as claimed are provided, for example, on pages 28-36. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

The Examiner maintains the assertion that "the term "antigen", "polypeptide" and "allergen" without the specific amino acid sequence or SEQ ID NO has no structure much less function." Applicants respectfully disagree with this assertion and this requirement for enablement. The term "antigen" is defined, for example, on pages 16 and 17, and many examples of antigens known in the art are provided, for example, on pages 43-50. Applicants respectfully submit that the

specification provides sufficient guidance to teach one skilled in the art how to make and/or use the claimed conjugates comprising an antigen.

With regard to the claimed polynucleotide, the Examiner states that "without the specific nucleotides [the polynucleotide] has no structure, let alone it is immunostimulatory." Office Action, page 9. The Examiner also points to the teaching of Yamada (Yamada et al. (2002) *J. Immunol.* 169:5590-5594) and Segal (Segal et al. (2000) *J. Immunol.* 164:5683-5688) in support of the rejection. Yamada indicates that some 5'-C, G-3' containing oligonucleotides have more immunostimulatory activity than others and does not discuss activity of the oligonucleotides when conjugated to an antigen. In the abstract on page 5683, Segal states that CpG ODN adjuvants "could potentially trigger autoimmune disease in a susceptible individual." Accordingly, the teachings of Yamada and Segal do not appear pertinent to the enablement of the claimed populations of conjugate molecules.

Applicants respectfully disagree that a description of an entire nucleotide sequence is necessary for the claimed polynucleotide. The amended claims are directed to conjugate populations in which the ISS-containing polynucleotide is greater than 6 and less than about 200 nucleotides in length and the ISS comprises the sequence 5'-C, G-3'. Applicants respectfully note that polynucleotides with immunostimulatory sequences containing the sequence 5'-C, G-3' have been described in scientific literature and in patents as active in cells of many mammalian species, including in humans. Thus, Applicants submit that the relative level of skill in the art is high.

Applicants note that the test for enablement is not whether a certain amount of experimentation is required to practice an invention, but rather whether the amount of experimentation is "undue." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants respectfully submit that the specification has provided a reasonable amount of guidance to the skilled artisan with respect to the direction in which the experimentation should proceed and that the

skilled artisan would be able to extend the teachings of the specification and the art to conjugate populations as claimed.

In addition, the Office has recently issued claims directed to methods of treating a subject through administering an immunostimulatory or immunomodulatory polynucleotide comprising an ISS, wherein the ISS comprises the sequence 5'-C, G-3'.[1] All of these patents have claimed priority dates earlier than or within months of the priority date of the instant application.

The claims in these patents are supported with experiments in which a limited number of 5'-C, G-3' containing oligonucleotides were tested for a particular activity or effect in a mouse model and, in some cases, on human cells in culture. Thus, in these cases, the Office has apparently deemed the state of the art such that the task of identifying nucleotides surrounding the core 5'-C, G-3' motif of an immunostimulatory polynucleotide as not an undue burden to the skilled artisan.

The court in *In re Wands* found that the enablement requirement was satisfied by a "disclosure [that] provides considerable direction and guidance on how to practice [the] invention and presents working examples," in view of the fact that "[t]here was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." *Id.* at 740. As outlined herein, the specification provides considerable guidance as to how to identify and make ISS-containing polynucleotides for use in the invention, how to identify and make or obtain the antigens as claimed, how to make the claimed conjugate populations and how to assess the composition and activity of the claimed conjugate populations. Thus, Applicants maintain that, following the reasoning in the *In re Wands* decision, the disclosure is adequate to enable the invention as claimed.

Applicants respectfully submit that the specification provides adequate guidance pertaining how to make and/or use the claimed conjugate populations. Accordingly, the pending claims are in compliance with the enablement requirements.

---

[1] See, for example, U.S. Pat. Nos. 6,613,751, 6,552,006, 6,534,062 and 6,498,148, submitted herewith.

Written Description

Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 74-75, 83-84, 86 and 90-107 were rejected as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner states that "there is insufficient written description about the structure associated with function of any population of conjugate molecules or composition mentioned above because the term "antigen", "allergen", "pollen allergen" and "polypeptide" without SEQ ID NO: have no structure." The Examiner also states that there "is inadequate written description about the nucleotides of any ISS that is "less than about 200 nucleotides in length", much less the undisclosed has immunostimulatory activity." Office Action, page 11. Applicants disagree with these assertions.

The written description requirement "may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure" and compliance with the requirement "is essentially a fact-based inquiry that will 'necessarily vary depending on the nature of the invention claimed.'" See *Amgen, Inc. v. Hoechst Marion Roussel, Inc. and Transkaryotic Therapies, Inc.*, USPQ 65 USPQ2d 1385 (Fed. Cir. 2003); *Enzo Biochem, Inc. v Gen-Probe, Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

The specification provides a description of many types and examples of known antigens appropriate for use in the claimed conjugate populations. Since the term antigen and examples of antigens are well known in the art as claimed in the present invention, Applicants submit that a skilled artisan would not require a specific amino acid sequence or SEQ ID NO to recognize possession of the claimed antigen conjugates.

Polynucleotides with lengths greater than 6 and less than about 200 nucleotides and containing an ISS comprising a 5'-C, G-3' sequence are well known in the art and are extensively

described in the specification such that a skilled artisan would recognize possession of the claimed polynucleotide conjugates. Applicants respectfully disagree with the assertion that a skilled artisan would not require a specific sequence or a SEQ ID NO to recognize possession of the polynucleotide in the claimed conjugate molecules.

The specification provides a description of sufficient, relevant, identifying characteristics of the claimed populations of conjugate molecules that one skilled in the art would recognize that the inventor had possession of the claimed invention when the application was filed. Applicants respectfully submit that the specification in combination with that known in the art adequately describes possession of the claimed genus to one skilled in the art. Thus, the pending claims are fully described in the specification as filed.

In view of the foregoing, Applicants respectfully submit that the written description requirement has been met.

New Matter

Claims 75, 83-84 and 86 were rejected for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

Support for claim 75 is found at page 23, lines 12-15 of the specification. The specification describes a conjugate molecule in which the "ratio of (i) average mass of ISS-containing polynucleotide to (ii) average mass of antigen is (i) about or alternatively at least about 35, 40 or 45 to (ii) about 40." Claim 75 is directed to conjugate molecules where (i) is at least 45 and so the ratio of (i)/(ii) is at least 45/40 or at least 1.1. Thus, claim 75 is described in the specification as filed and does not contain new matter.

Accordingly, the pending claims are in compliance with the written description requirement.

In sum, Applicants submit that the pending claims fall within the subject matter that is enabled and described by the specification as filed. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

Rejection under 35 U.S.C. §112, second paragraph

Claims 1, 7, 50-51, 60-61, 71-72, 83-84 and 90-93 were rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicants respectfully traverse this rejection.

Although Applicants believe that the claims were sufficiently definite when considered in view of the specification and the understanding of those of skill in the art, Applicants have attempted to respond to the concerns of the Examiner in order to enhance clarity and to facilitate disposition of the present case.

Claims 1, 7, 50-51, 60-61 and 90-93 have herein been canceled. Thus, rejection of these claims is moot.

With regard to claims 71, 72, 83 and 84, Applicants respectfully point out that the sequence recited in claim 71 includes the sequence recited in claim 63 plus additional nucleotides. Thus, dependent claim 71 is narrower in scope than claim 63. Also, the sequence recited in claim 83 includes the sequence recited in claim 75 plus additional nucleotides. Thus, dependent claim 83 is narrower in scope than claim 75. Accordingly, the sequences of the dependent claims 71 and 83 have proper antecedent basis in independent claims 63 and 75, respectively.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. §102(b)

Claims 1-3, 7-8, 50-51, 60-61, 63, 71-72, 75, 83-84, 86 and 90-107 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by WO 98/16247 publication (Carson et al., "Carson"). Applicants respectfully traverse this rejection.

As an initial matter, although Applicants respectfully traverse this rejection, claims 1-3, 7, 8, 50, 51, 60, 61, 87, 90-93 and 102-105 have herein been canceled without prejudice or disclaimer.

For a claim to be anticipated by a reference, that reference must disclose each and every element of the claim.

The Examiner states that Carson "teaches that the concentration of the oligonucleotide (ISS) to antigen is 5:1." The Examiner then asserts that the conjugate molecules of Carson have "the same extend of conjugation" as the claimed molecules. Office Action, page 18. Applicants respectfully disagree with the assertion that Carson teaches the extent of conjugation as claimed in the instant invention.

In claim 63, the extent of conjugation in the population of conjugate molecules provides an average of at least 5.5 ISS-containing polynucleotides per antigen molecule. The Examiner states that claim 63 is rejected because it "would include the reference 5 ISS containing polynucleotides per one antigen molecule." Office Action, page 18.

Applicants respectfully point out that an average of at least 5.5:1 is clearly not the same as 5:1 and the conjugate molecules of the instant invention are different that those of Carson. To provide an average of at least 5.5:1, the extent of conjugation in the claimed invention is clearly greater than the reference conjugation. Although the Examiner asserts that "the disparity in the ISS to antigen ratio may be related to the different techniques" used for quantification, Applicants point out that differences in the ISS to antigen ratios is due to the claimed invention being different than that taught in Carson.

In addition to that stated above regarding the concentration of ISS to antigen, the Examiner also describes the conjugates of Carson as containing the "mass ratio of ISS to antigen is 5:1." Office Action, page 18. Applicants note that the average mass is not the same as the number of molecules and that a particular concentration of molecules does not necessarily correlate to the same mass ratio of molecules. Applicants submit that a concentration of ISS to antigen of 5:1 does not necessarily translate to an ISS to antigen mass ratio of 5:1, as stated by the Examiner as the basis for the rejection of claim 75.

In claim 75, the extent of conjugation in the population of conjugate molecules provides an average ratio of average mass of ISS-containing polynucleotides to average mass of antigen of at least 1.1. Applicants submit that the teaching of Carson does not necessarily translate to an ISS to antigen mass ratio of at least 1.1. Applicants respectfully submit that the Office Action has not provide fact or sound technical reasoning to support these statements and thus to support this rejection.

Since Carson does not teach every element of the pending claims, Carson does not anticipate the claimed invention.

Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b).

CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001500.

Dated: October 31, 2003

Respectfully submitted,

By Karen R Zachow

Karen R. Zachow, Ph.D.
Registration No.: 46,332
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304
(858) 720-5191